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Direct-Type Catalytic Three-Component Mannich Reactions Leading to an Efficient Synthesis of α,β-Diamino Acid Derivatives

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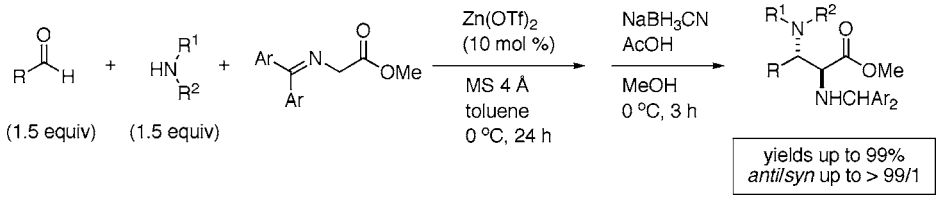
ABSTRACT



The first example of the Lewis acid-catalyzed three-component direct-type Mannich reaction of simple aromatic and enolizable aliphatic aldehydes, secondary amines, and glycine derivatives is described. The procedure is highly atom economical and can be performed in a simple one-pot operation under mild conditions to afford a wide variety of synthetically important *anti*-α,β-diamino ester derivatives in high yields with high diastereoselectivities.

The Mannich reaction is one of the most important carbon−carbon bond forming reactions in organic synthesis.[1] In the classical intermolecular Mannich reaction, three components, an aldehyde, an amine, and an α-acidic carbonyl compound, react directly to form a β-amino carbonyl compound (Mannich base).[2] Despite the potential utility of this reaction, traditional protocols require somewhat harsh conditions and long reaction times leading to competition from undesired side reactions. Furthermore, these early three-component reactions suffered from a number of serious limitations, in that generally only formaldehyde could be used as a nonenolizable aldehyde precursor of the iminium ion; additionally, only aldehydes or ketones can be employed as enolate precursors, as other carbonyl compounds such as esters are inert to aminomethylation. In recent years, a number of groups have developed a range of methods to obviate the problems associated with the direct-type Mannich reactions and have sought to extend the methodology to asymmetric varients.[3] Most of these have focused on utilizing preformed imines or iminium salts and preformed enolate equivalents such as silyl enol ethers or silyl ketene acetals which are much more reactive than their respective parent carbonyl compounds.[4] Although such developments, widely

(1) Mannich, C.; Krosche, W. *Arch. Pharm. (Weinheim, Ger.)* **1912**, *250*, 647.

(2) For reviews of the subject: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (b) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 923−961. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(3) For recent examples of the metallocatalytic enantioselective indirect Mannich reaction, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (b) Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem.−Eur. J.* **2002**, *8*, 4185. (c) Kobayashi, S.; Ueno, M. In *Comprehensive Asymmetric Catalysis, Supplement I*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5. (d) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734. (f) Josephsohn, N. S.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 2711. (g) Akullian, L. C.; Snapper, M. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532 and references therein.

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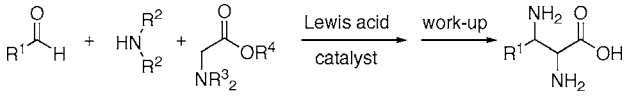
known as *indirect-type* Mannich reaction protocols because of their reliance on the use of preformed key intermediates rather than their generation in situ, represent an important advance in the synthetic utility of the Mannich reaction, they suffer from the obvious drawback of the necessity for isolation and purification of these preformed imine and enolate equivalents.

A further improvement in the methodology has been realized in the development of metal catalyst systems[5] and organocatalysts[6] that promote the so-called *direct-type catalytic* Mannich reaction which makes use of unmodified aldehydes or ketones as nucleophiles. However, these procedures still largely rely on the use of highly activated or aniline-derived imines prepared and isolated beforehand, and corresponding examples of *catalytic asymmetric versions* of direct-type three-component Mannich reactions in which all the reactive entities are formed in situ *catalytically* are quite limited.[7] Moreover, to the best of our knowledge, no examples of the three-component transformation employing esters as nucleophiles have been reported, presumably because of inadequate acidity of the proton at the α-position of the ester moiety.[8] Clearly then, there is a need for alternative protocols which address the shortcomings of currently available methods and extend the range of substrates and nucleophiles that can funtion in the reaction.

Herein, we describe the first Lewis acid-catalyzed direct-type three-component Mannich reactions of glycine ester derivatives with iminium salts generated in situ from secondary amines. This reaction provides an efficient synthetic approach to α,β-diamino acid derivatives, which are important structural components of many natural products and medicinal agents (Scheme 1).[9]

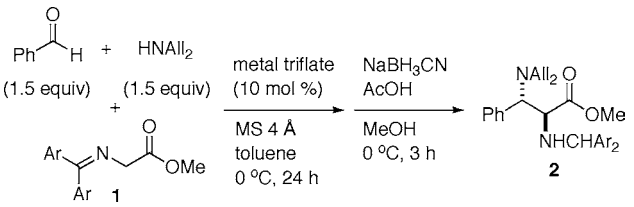
Scheme 1. Direct-Type Catalytic Three-Component Mannich-Type Reactions Leading to α,β-Diamino Acid Derivatives



Previously, we reported the Lewis acid-catalyzed direct addition of glycine derivatives to enamines.[10] In the course of our investigations into expanding the scope of this reaction, we found that *N*-(diphenylmethylene)glycinates **1** activated by a metal triflate such as $Zn(OTf)_2$ worked as effective nucleophiles in the Mannich reaction of iminium ions derived from enamines to afford the corresponding α,β-diamino esters in high yields.

We expected that this system could also be applied to three-component reactions using aldehydes, secondary amines, and glycine derivatives **1** (Table 1). After initial investigations, we discovered the desired direct-type three-component reactions took place in the presence of a metal triflate and molecular sieves (MS). Because the initial product with a

Table 1. Direct-Type Catalytic Three-Component Mannich Reactions of Glycine Derivatives **1**



entry	glycine derivative	metal triflate	product	yield (%)	anti/syn
1	**1a** (Ar = Ph)	$Sc(OTf)_3$	**2a**	10	69/31
2	**1a**	AgOTf	**2a**	22	59/41
3	**1a**	CuOTf·1/2PhMe	**2a**	20	65/35
4	**1a**	$Cu(OTf)_2$	**2a**	28	65/35
5	**1a**	$Zn(OTf)_2$	**2a**	66	86/14
6	**1b** (Ar = 4-ClC_6H_4)	$Zn(OTf)_2$	**2b**	62	90/10
7	**1c** (Ar = 4-$CF_3C_6H_4$)	$Zn(OTf)_2$	**2c**	97	93/7

(4) For examples, see: Silyl enol ethers: (a) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (b) Enders, D.; Oberbörsch, S.; Adam, J. *Synlett* **2000**, 644. Enamines: (c) Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689. (d) Zarghi, A.; Naimi-Jamal, M. R.; Webb, S. A.; Saidi, M. R.; Ipaktschi, J. *Eur. J. Org. Chem.* **1998**, *197*, 7. Boron enolates: (e) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. Lithium enolates: Palomo, C.; Oiarbide, M.; Gonzalez-Rego, M. C.; Sharma, A. K.; Garcia, J. M.; Gonzalez, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063.

(5) Almost all reports of the direct Mannich-type reaction published to date use activated imines or aniline-derived imines: (a) Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161. (b) Shida, N.; Kubota, Y.; Fukui, H.; Asao, N.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5023. (c) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (d) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (e) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (f) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (g) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777.

(6) With proline derivatives: (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (c) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, 3667. (e) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (f) Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, 8669. (g) Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433. (h) Guillena, G.; Hita, M.d.-C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027. (i) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas; C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040. (j) Rodríguez, B.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 2888. With cinchona alkaloids: (k) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (l) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. With Brønstead acids: (m) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (n) Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079.

(7) (a) Yamazaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (c) List, B.; Pojatliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (d) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (e) Chowdari, N. S.; Suri, J. T.; Barbas; C. F., III. *Org. Lett.* **2004**, *6*, 2507. (f) Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc.* **2004**, *126*, 15942. (g) Córdova, A. *Chem.−Eur. J.* **2004**, *10*, 1987. (h) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.−Eur. J.* **2005**, *11*, 7024. (i) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

benzophenone imine moiety was somewhat unstable under acidic conditions, it was isolated as the more stable amine derivative **2a**.

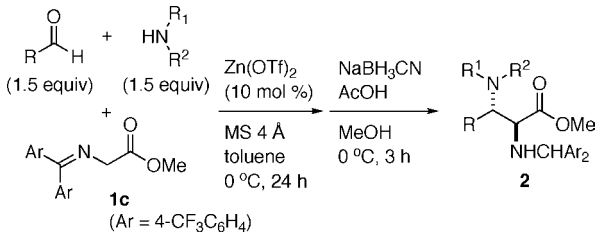
When $Sc(OTf)_3$ (10 mol %) was employed as a catalyst in the presence of 4 Å MS, the reaction of benzaldehyde, diallylamine ($HNAll_2$), and methyl *N*-(diphenylmethylene)-glycinate **1a** proceeded only sluggishly in toluene at 0 °C to afford the corresponding addition product which was subsequently converted to diamino ester derivative **2a** (10% yield, anti/syn = 69/31, Table 1, entry 1). Although this reaction provided the product in only low yield and poor selectivity, it should be borne in mind that the reaction involves a multistep sequence of (1) addition of the diallylamine to the benzaldehyde, (2) dehydrative iminium formation, (3) formation of the glycinate-derived enolate, and (4) the Mannich reaction of these two species to give the desired α,β-diamino ester product, in a single pot.

Encouraged by this result, we screened a number of metals for their utility in the transformation. Although, in general, the desired product was still only obtained in low yield in the case of AgOTf, CuOTf, or $Cu(OTf)_2$ (entries 2−4), a significant improvement in yield and diastereoselectivity (66%, anti/syn = 86/14)[11] was realized when $Zn(OTf)_2$ was employed in the reaction (entry 5). It is of great interest that the introduction of electron-withdrawing substituents at the para position of the benzophenone moiety of **1** improved the diastereoselectivity of the reaction. In the case of the chloro-substituted glycine derivative **1b**, the anti/syn ratio was increased to 90/10, although the yield was moderate (entry 6). Furthermore, when a 4-trifluoromethyl group was introduced, the reaction proceeded smoothly to afford the corresponding α,β-diamino ester derivative **2c** in excellent yield with high anti selectivity (97% yield, anti/syn = 93/7, entry 7).

With these results in hand, attention moved to the reactions of other aldehydes, and the results are summarized in Table 2. When a variety of substituted benzaldehydes bearing electrodynamically neutral or electron-donating groups were employed, the reactions proceeded smoothly to give the desired α,β-diamino ester derivatives in high yields with high anti selectivities (entries 1−9), although the reactivity of 4-chlorobenzaldehyde was rather low compared to that of others (entry 10).

Naphthaldehydes also proved to be good substrates in the reaction, giving the corresponding products in excellent yields with high diastereoselectivities (entries 12 and 13). In the reaction of the heteroaromatic aldehyde thiophencarboxaldehyde, a slight decrease of diastereoselectivity was observed because of disadvantageous interactions between the heteroaromatic ring and the catalyst, whereas the corresponding Mannich adduct itself was obtained in good yield (entry 14). It should be noted that aliphatic aldehyde 3-phenylpropanal, which would be easily enolized under the conditions required for classical Mannich reactions leading

Table 2. Direct-Type Catalytic Three-Component Mannich Reactions of Glycine Derivatives **1c** with Various Secondary Amines and Aldehydes



entry	R	HNR_1R_2	product	yield (%)	anti/syn
1	Ph	$HNAll_2$	**2c**	97	93/7
2	Ph	$HNBn_2$	**2d**	31	88/12
3	Ph	HNBnMe	**2e**	74	91/9
4	Ph	$HNnPr_2$	**2f**	80	91/9
5	Ph	piperidine	**2g**	73	90/10
6	4-MeC_6H_4	$HNAll_2$	**2h**	92	97/3
7	3-MeC_6H_4	$HNAll_2$	**2i**	95	92/8
8	2-MeC_6H_4	$HNAll_2$	**2j**	98	96/4
9	4-$(MeO)C_6H_4$	$HNAll_2$	**2k**	99	95/5
10	4-ClC_6H_4	$HNAll_2$	**2l**	77	95/5
11	3,5-$(MeO)_2C_6H_3$	$HNAll_2$	**2m**	95	>99/1
12	2-naphthyl	$HNAll_2$	**2n**	99	98/2
13	1-naphthyl	$HNAll_2$	**2o**	97	97/3
14	3-thienyl	$HNAll_2$	**2p**	72	91/9
15[a]	$PhCH_2CH_2$	$HNAll_2$	**2q**	96	61/39

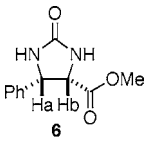
[a] Glycine derivative **1a** was used.

(8) The indirect and direct-type Mannich reaction has been carried out with ester equivalents using isolated imines as electrophiles: (a) Marigo, M.; Kjærsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem.−Eur. J.* **2003**, *9*, 2359. (b) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367. (c) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (d) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365. (e) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525.

(9) For recent examples of syntheses of biologically important compounds using the asymmetric catalytic Mannich reactions, see: (a) Palomo, C.; Oiarbide, M.; Landa, A.; Gonzalez-Rego, M. C.; Garcia, J. M.; Gonzalez, A.; Odriozola, J. M.; Martin-Pastor, M.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 8637. (b) Jacobsen, M. F.; Skrydstrup, T. *J. Org. Chem.* **2003**, *68*, 7112. (c) Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. *Org. Lett.* **2003**, *5*, 3639. (d) Lal, B.; Gund, V. G.; Baban, N.; Gangopadhyay, A. K. *Bioorg. Med. Chem.* **2004**, *12*, 1751. (e) Rougnon-Glasson, S.; Tratrat, C.; Canet, J.-L.; Chalard, P.; Troin, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1561. (f) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243. (g) Brummond, K. M.; Hong, S.-P. *J. Org. Chem.* **2005**, *70*, 907. (h) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784. (i) Lanter, J. C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett.* **2005**, *7*, 5905. (j) Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390. (k) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 5756 and references therein.

(10) Kobayashi, J.; Yamashita, Y.; Kobayashi, S. *Chem. Lett.* **2005**, *34*, 268.

(11) The anti structure of the major isomer was established by comparison of coupling constants of the cyclic urea **6** derived from the major isomer of **2a** (*J*ab = 9.8 Hz) with the literature value (*J*ab [anti] = 9.7 Hz; *J*ab [syn] = 4.6 Hz) for the same compound:



6

*J*ab = 9.8 Hz

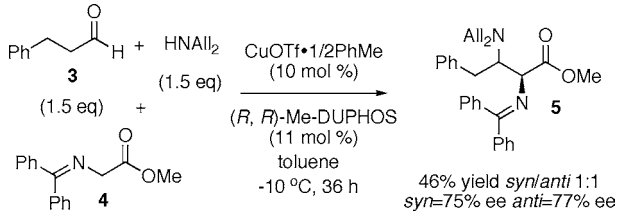
Lee, S.-H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139.

to undesirable side reactions, was also amenable to the reaction conditions, giving the desired compound in high yield (96% yield, entry 15).

Although the diastereoselectivity of this reaction was not particularly high (anti/syn = 61/39), aliphatic aldehydes were sufficiently reactive under these conditions so that electron-withdrawing groups at the para position of the benzophenone moiety of **1** were not needed to obtain high yields.

Finally, we investigated the possibility of conducting a catalytic *asymmetric* version of the three-component Mannich reaction. It was found that in the reaction of 3-phenylpropanal **3** with *N*-(diphenylmethylene)glycinate methyl ester **1a** use of (*R*,*R*)-Me-DUPHOS in combination with CuOTf·1/2PhMe (10 mol %) at moderately low temperature afforded the chiral *N*,*N*-diallylamine **5** in moderate yield as an equimolar mixture of syn and anti isomers in 75% ee and 77% ee, respectively (Scheme 2).

Scheme 2. Asymmetric Catalytic Three-Component Mannich Reaction Mediated by CuOTf



In summary, we have successfully demonstrated the first Lewis acid-catalyzed direct-type three-component Mannich reaction of simple aldehydes, secondary amines, and glycine derivatives. This method represents an important addition to the Mannich-based methodology available to synthetic chemists and supersedes the classic three-component Mannich reaction system, in that it functions with simple aromatic and enolizable aliphatic aldehydes other than formaldehyde as iminium precursors and allows the use of esters as carbonyl components (instead of ketones or aldehydes) in the three-component reaction for the first time. Furthermore, the current protocol is a highly atom-economical process and can be carried out in a simple one-pot operation under mild conditions. In addition, reactions of various aromatic aldehydes proceed smoothly to afford the corresponding *anti*-α,*β*-diamino ester derivatives in high yields with high diastereoselectivities. The reaction with an aliphatic aldehyde however gave the product in lower diastereoselectivity. Such orthogonally protected diamino ester derivatives can be useful as α,*β*-diamino carbonyl units, which have recently attracted much attention from several scientific standpoints. Further investigations aimed at improving yields and selectivity of the catalytic asymmetric process and at clarifying the reaction mechanism are now in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Typical experimental procedure and spectroscopic data for compounds **2a**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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